AWARD NUMBER: W81XWH-15-1-0441

TITLE: Incorporation of Novel MRI and Biomarkers into Prostate Cancer Active Surveillance Risk Assessment

PRINCIPAL INVESTIGATOR: Michael A. Liss, M.D., M.A.S.

CONTRACTING ORGANIZATION: University of Texas Health Science Center
San Antonio, TX 78229

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14. ABSTRACT

The purpose of this research is to improve the baseline and longitudinal risk assessment of prostate cancer patients electing active surveillance (AS) as their management strategy. Our broad objective is two-fold: [1] to improve the ability to select candidates who safely choose active surveillance as a prostate cancer management strategy and [2] to improve current monitoring for progression of prostate cancer. We subsequently aim to improve non-invasive means to monitor prostate cancer and improve the ability to decide when to intervene with therapeutic intent. Additionally we seek to reduce the number of biopsies, in turn reducing the morbidity of the AS strategy.

15. SUBJECT TERMS
Prostate Cancer, Imaging, Magnetic Resonance Imaging, Active Surveillance, Prostate Biopsy, Diffusion weighted imaging, PSA, Biomarkers, Risk calculator

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Table of Contents

Page

1 INTRODUCTION:

Prostate cancer is a prevalent disease among men with over 230,000 new cases reported each year. More than two-thirds of these men are diagnosed with low-risk prostate cancer (Gleason 6 or less). An increasing number of men in this low-risk group are choosing Active Surveillance (AS) over aggressive treatment thereby subjecting themselves to serial prostate biopsies. Prostate biopsies can be inaccurate and cause significant pain, bleeding, infection, and anxiety over the years men with low-risk prostate cancer are followed.

Improving non-invasive techniques to monitor prostate cancer status will enhance clinical decision making on timing of therapeutic interventions. This should result in a decrease in serial biopsies thereby reducing the overall morbidity of men who choose the active surveillance strategy.

This grant is a training award. I have engaged my mentors, enrolled in courses and conferences to augment my knowledge of translational science and MRI imaging, and I have developed and am managing my first clinical trial. My long-term goal is to become a leader in the field of urology as a clinical researcher. My focus is to improve the lives of patients with prostate cancer by implementation of imaging and biomarkers at the point of care.

2 KEYWORDS:

Prostate Cancer
Active Surveillance
Prostate Biopsy
Imaging
Magnetic Resonance Imaging
Diffusion weighted imaging
PSA
Biomarkers
Risk calculator

3 ACCOMPLISHMENTS:

What were the major goals of the project?
This Prostate Cancer Physician Training Award is divided into three integrated components, **training, mentorship, and research,** each of which has its own set of specific major goals.

The **training component** is comprised of three goals that are integral in the preparation for a career in clinical research. These goals are 1) training in T1 translational research; 2) training in the development and management of clinical trials, and 3) training in MRI biomarker and risk assessment techniques. Translational

research training includes formal coursework to obtain the Certificate in Translational Research as well as engaging in the Translational Research Awareness Program (TRAP). Clinical trials training includes participating in the GU working group meetings at the cancer center, completion of a young investigators training course, and involvement in ongoing clinical trials with Dr. Thompson. The third goal includes additional training in MRI imaging through a series of prostate specific imaging courses as well as several MRI specific formal courses offered at UTHSCSA. In order to gain a working knowledge of how imaging is incorporated into the overall clinical diagnosis and treatment plans, I will attend the semi-annual **SWOG Imaging committee** meetings along with the general SWOG meetings.

The **mentorship** component included Dr. Ian Thompson as my Mentor, Dr. Peter Fox as my Co-Mentor, and Dr. Robin Leach as a collaborating mentor. Each mentor is an expert in one of the integral focus areas of this award.

Dr. Thompson is a leader in prostate cancer clinical research and Director of the Cancer Therapy and Research Center (CTRC) which is one of four NCI designated cancer centers in Texas. In addition to basic mentoring tasks, we have identified four sources of mentorship in particular to my career, which include opportunities at the CTRC, SWOG, PASS, and the SABOR clinical trials.

Dr. Fox is a leader in imaging research and is the Director of the Research Imaging Institute. He has a working relationship with my previous MRI Mentors at UCSD where I received my fellowship training and completed preliminary studies using the novel restriction spectrum imaging (RSI) MRI techniques.

Dr. Leach is an expert in Biomarker evaluation as well as the Director of the Biobanking and Genome Analysis Research Core at UTHSCSA. My mentorship plan includes regularly scheduled individual and group meetings with each mentor as well as an advisory committee that includes Drs. Thompson, Fox, and Leach to oversee my progress through the DOD Prostate Cancer Physician Research Training program.

The **research** component is a clinical research project that investigates a novel MRI technique called Restricted Spectrum Imaging (RSI) in men undergoing active surveillance for low risk prostate cancer. Our broad objective is two-fold: [1] to improve the ability to select candidates who safely choose active surveillance as a prostate cancer management strategy and [2] to improve current monitoring for progression of prostate cancer. We subsequently aim to improve non-invasive means to monitor prostate cancer and improve the ability to decide when to intervene with therapeutic intent. Additionally we seek to reduce the number of biopsies, in turn reducing the morbidity of the active surveillance strategy.

Our specific aims were:

Aim 1: Prostate MRI to predict Progression on Active Surveillance.
Aim 2: Biomarker testing to predict active surveillance outcomes.
Aim 3: Incorporation of Imaging and Biomarker data into the PROMISS calculator.

What was accomplished under these goals?

Training:

I was accepted into the **Certificate in Translational Research** program on 12/14/2015 and completed MEDI 6101 Topics in Translational Science in the Spring 2016 semester. I am enrolled in MEDI 6101 Topics in Translational Science (part 2) and MEDI 5070 Responsible conduct of Patient-Oriented Clinical Research. I have reviewed 10 articles (17%, 10/60) of the **Translational Researcher Awareness Program** (TRAP) with Dr. Thompson.

I became a member of the Cancer Therapy and Research Center (CTRC). I have been heavily involved in the GU Working group and have attended all meetings at the CTRC. In addition, I have joined SWOG and attended both semi-annual in 2016. I attend both the GU Committee weekly working group meetings and the monthly general Genito-urinary meeting where leaders in the field discuss new and continuing clinical trials. Fortunately, my involvement has lead to my election as the site principal investigator for SWOG which requires me to represent UTHSCSA at the bi-annual Board of Governors meetings. In addition, I have been involved in the Prostate Active Surveillance Study (PASS) and have published a first author manuscript with the group entitled "A diagnosis of prostate cancer and pursuit of active surveillance is not followed by weight loss: potential for a teachable moment" published in *Prostate cancer and prostatic diseases* in July 2016. I have also become involved in a second ongoing clinical research study entitled San Antonio Biomarkers of Risk (SABOR) for prostate cancer. Under the guidence of Dr. Thompson, I have published a first auther paper entitled "Prevalence of Isolated "Pre-Malignant" Lesions on Prostate Biopsy in a Racially Diverse Community Screened Cohort" in the *Open Journal of Urology* in 2015.

An important part of my training plan is developing my ability to train others. I am the leader of the Urologic Oncology morning conference every other Friday and hold regular journal clubs for our Urology residents. I have created an Active Surviellance clinic at the South Texas Veterans Hospital in San Antonio where I see a majority of men with prostate cancer and can now enroll patients directly from this clinic into my clinical trials.

I have received additional training in MRI imaging by attending The ARRS Prostate MRI Symposium in Austin Texas on Feburary 26, 2016. This Symposium provided not only many inciteful lectures but also offered an opportunity to meet with leaders in the Imaging field such as Dr. Peter Pinto. I was fortunate to be able attend this meeting with two of my collegues in Radiology as this shared experience has signficantly improved our communications and readings of MRI scans together. We hold monthy Prostate MRI conferences where we read new MRI's together and review MRI targted biopsies to improve quality of the scans and reads. In addition, I attended the SWOG Imaging Committee meeting on 9/16/2016 for a lecture on how MRI has been incorporated into colorectal cancer clinical trials.

Mentoring:

Drs. Thompson and Leach have been integral and very involved in the mentoring process. We meet nearly every Monday morning for 1-2 hours with our research group. Drs. Thompson and Leach are preparing a prostate SPORE applicaton to be submitting to the NCI in January of 2017. I will be a co-investigator on their Project 1 which attempts to identify high grade prostate cancer in men with low PSA. My RSI imaging will be an important component of their application and I am working closely with them to generate critical prelimiary data. In addition to these activities, Dr. Thompson has provided opportunities within CTRC and SWOG for involvement and leadership roles. I have been involved with the SABOR and PASS clinical trials under his guidence and mentorship as well. My co-mentor, Dr. Peter Fox, has been very helpful with navigating the Research Imaging Institute and providing a connection with a fantastic medical physicisit, Dr. Geoffery Clarke. We experienced some delays with implementation due to having a different MRI hardware system (Seimens) at UTHSCSA then at UCSD (GE). Dr. Fox was instrumental in facilitating the resolution of this issue in as timely a manner as possible. Dr. Robert Svatek is a non-formal advisor and has been very helpful navigating the intracites of clinical research and he is now activating his first national cooperative group clinical trial, SWOG S1602 with BCG vaccination in bladder cancer. Additionally, my chairman Dr. Ronald Rodriguez has been very supportive of my research and trainng grant has accomodated my clinical schedule for protected time to ensure I meet the goals of my grant and career development.

Research:

We have successfully implemented the acquisition portion of the RSI MRI at UTHSCSA. There were some initial delays in implementation due to the different MRI hardware systems at UCSD and UTHSCSA. Additional time was needed to modify the sequences and then do practice scanning to ensure the images were consistent across the two systems. Under the guidance of Dr. Clarke, I was able to correct the scanner differences. We then underwent practice scanning for comparison and quality control from UCSD. The images were uploaded utilizing XNAT (Extensive Neuroimaging Archive Toolkit). UCSD then viewed and analyzed our images securely and remotely and we were able to ensure the consistency of the scans and readings across the two hardware systems.

The project received UTHSCSA IRB approval (HSC20150160H) and we began enrolling subjects on 2/5/2016. Biologics (blood and urine) were collected on all subjects for application of Aim 2 biomarkers. We also have secured the material transfer agreement with Dr. Dobi at the Center for Prostate Disease Research for application of the Nanostring technology to our biopsy samples. Utilizing the MRI, without implementation of the RSI component, we have identified a sensitivity of 87% and specificity of 47% in the 9 patients that have complete data. The negative predictive value of MRI as a biomarker is 75% in men on active surveillance. We are currently working on the software component of the RSI MRI that will analyze the scans and allow comparison to standard MRI.

Background and objectives

Active surveillance is a strategy used to monitor low risk prostate cancer in order to delay or avoid aggressive therapies with the option to intervene yearly in the disease process with curative intent if progression is detected. Unfortunately, the initial and secondary prostate biopsies suffer from a 30% sampling error. Progression is usually detected by repeating the prostate biopsy, in some cases yearly. Prostate biopsies can cause significant pain, bleeding, infection, and anxiety. The primary objective of this project is to investigate if a novel screening MRI can predict prostate biopsy outcomes and eventually replace the prostate biopsy as the primary means to follow these patients. The secondary purpose is to use biomarkers from blood, urine, or prostate tissue to identify those men who are likely to progress while on active surveillance.

Methods

Our primary population is men who are diagnosed with prostate cancer and choose active surveillance. We plan to enroll 160 subjects to undergo a prostate MRI prior to their TRUS prostate biopsy. Both conventional MRI with IV gadolinium contrast and Restriction Spectrum Imaging (RSI) techniques will be employed (Figure 1). Images will be evaluated using a five-point scale (PI-RADS) to determine suspicion of clinically significant prostate cancer (Figure 2). PI-RADS will also be used to grade the RSI images with secondary radiology review. After the MRI, the patient will undergo targeted and template prostate biopsy and pathology compared to PI-RADS (Figure 3). Other study endpoints will include Gleason 6 tumor (low-grade) or a negative biopsy. After pathologic review the paraffin embedded tissue will be sent the CPDR in Rockville, MD for the Aim 2b NanoString technology investigation.

Figure 1

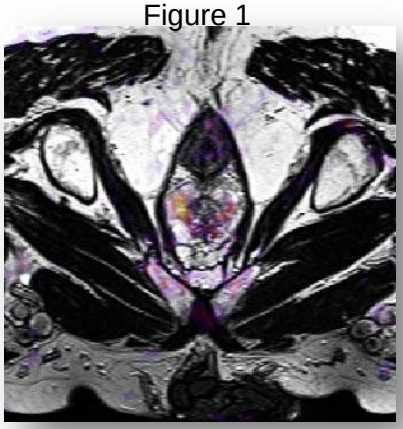


Figure 1: RSI-MRI imaging performed at UTHSCA Research Imaging Institute. Yellow/Red indicates high suspicion of tumor.

Figure 2

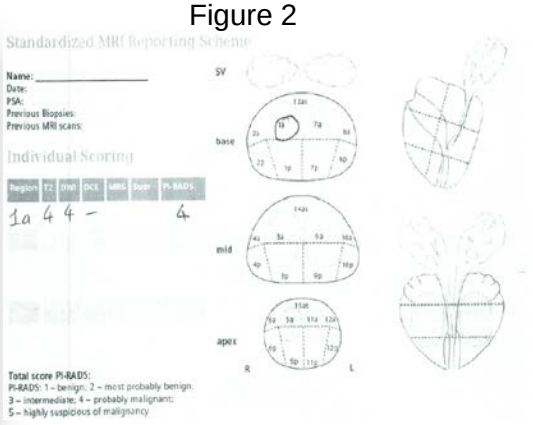


Figure 2: Radiology reading report in the same patient indicated a lesion in the same location given a PI-RADS 4 score.

Figure 3

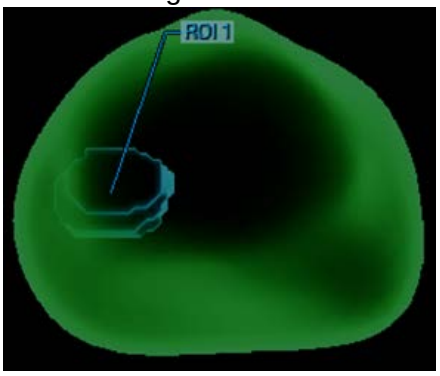


Figure 3: Three-dimensional rendering of the prostate utilizing the RSI-MRI then DynaCAD software for targeted prostate biopsy with Gleason 3+4 cancer.

Results To Date

To date we have completed the IRB protocol and attained approval for imaging in men undergoing active surveillance for prostate cancer who have an upcoming prostate biopsy. We have enrolled 23 subjects to obtain an MRI and undergo cognitive or MRI-Fusion targeted prostate biopsy from 2/5/2016 to present. Of these 23 subjects, fifteen have had an MRI and completed their biopsy. Two subjects dropped out of the study as screening fails at the MRI scanner (Elevated creatinine and Claustrophobia, respectively).

Of the 15 patients that completed the study, four MRI scans were read as “no lesions found”. Of these only 1 had a small focus of low-grade prostate cancer, which is clinically insignificant. On the other hand 8 of 9 (89%) PI-RADS 4 lesions were positive for cancer on prostate biopsy. The overall operating characteristics include a sensitivity of 89%, specificity of 50%, Positive predictive value of 72% and negative predictive value of 75%.

Table 1

	False Positive	**False Negative**	**True Positive**	**True Negative**
	3	1	8	3
Gleason	Negative PI-RADS 4	3+3	3+3 PI-RADS 4	Negative
	Negative PI-RADS 3		3+3 PI-RADS 4	Negative
	Negative PI-RADS 3		3+3 PI-RADS 3	Negative
			4+4 PI-RADS 4	
			4+4 PI-RADS 5	
			3+3 PI-RADS 4	
			3+3 PI-RADS 3	

Conclusions

We have successfully implemented our Prostate MRI study at the University of Texas HSC San Antonio. From our preliminary results, PI-RADS 4 and 5 lesions are more significant findings on prostate biopsy. Importantly a negative MRI indicates no cancer or very low risk cancer is present and may guide future biopsy decisions. We look forward to continuing this research in order to obtain a better power to more accurately describe our results.

Impact statement

Our research is directed towards improving the quality of life of prostate cancer patients in the form of reduction of prostate biopsies and more accurate selection of active surveillance candidates.

What opportunities for training and professional development has the project provided?
The DOD IMPACT meeting was very successful for me. It provided an opportunity to meet with other prostate cancer researchers and specifically those in MRI imaging. We are now planning on collaborative interactions. Moreover, the grant provided a validation of the research I am doing and my dedication to translational science. Since receiving this training award, I have been elected to serve as the **SWOG site Principal Investigator** and have also been appointed as the **Medical Director for Clinical Research** at University Hospital in San Antonio, Texas.

How were the results disseminated to communities of interest?
My poster presentation was accepted for the DOD IMPACT meeting in Baltimore, MD on August 5, 2016.

What do you plan to do during the next reporting period to accomplish the goals?
My plans for the next period include:

a. Implement RSI MRI software component
b. Continue subject enrollment
c. Aggressive pursuit of funding for MRI and biomarker studies
d. Continue TRAP article review with mentors
e. Attend national MRI conference / workshop
f. Continue Certificate in Translational Science coursework

4 IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
The project is still ongoing. Based on our current subjects, the MRI seems to have value in men with low-grade prostate cancer on active surveillance. We are now researching how to standardize the imaging across multiple hardware systems, reduce the cost of the imaging, and provide faster results to providers and patients. We plan to change the clinical management of men with low-grade prostate cancer by incorporating imaging as a standard procedure in follow up visits thereby reducing unnecessary interventions such as prostate biopsies and the morbidities associated with those interventions.

What was the impact on other disciplines?
The core of our project is a joint venture between Urology and Radiology. Both fields will be impacted by the study as it may set a new standard for prostate cancer treatment. We also feel that a standardized, non-invasive scan would set a baseline quality study that could be compared across scanners and institutions. Additionally, we will investigate imaging as a biomarker and incorporate into a risk calculator which will impact the field of prostate cancer biomarkers and prevention research. The knowledge gained from this project can be applied to research on cancers in other organ sites.

What was the impact on technology transfer?
Nothing to report

What was the impact on society beyond science and technology?
If successful, this project has the potential to change the standard of care of prostate cancer in daily clinical practice and long term management. By focusing on non-invasive techniques, patient comfort and individualized risk assessment we hope to change patient behaviors in order to increase compliance with long term treatment / management plans. These non-invasive techniques can reduce morbidities and increase the quality of life for patients on active surveillance treatment plans.

5 CHANGES / PROBLEMS:

Changes in approach and reasons for change?
Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them?
Nothing to Report

Changes that had a significant impact on expenditures?
Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents?
Nothing to Report.

Significant changes in use or care of human subjects: No Changes
Significant changes in use or care of vertebrate animals: Not Applicable
Significant changes in use of biohazards and/or select agents: No Changes

6 PRODUCTS:

Publications, conference papers, and presentations

Journal publications.

Liss MA, Schenk JM, Faino AV, Newcomb LF, Boyer H, Brooks JD, et al. A diagnosis of prostate cancer and pursuit of active surveillance is not followed by weight loss: potential for a teachable moment. Prostate cancer and prostatic diseases. 2016 Jul 19. PubMed PMID: 27431498. acknowledgement of federal support (yes).

Liss MA, Ankerst, D., Zapata, D., Hernandez, J., Leach, R.J. Thompson, I.M. Prevalence of Isolated “Pre-Malignant” Lesions on Prostate Biopsy in a Racially Diverse Community Screened Cohort. Open Journal of Urology. 2015;5(12). acknowledgement of federal support (yes).

Books or other non-periodical, one-time publications.
None

Other publications, conference papers, and presentations
Poster presentation entitled ” Incorporation of Novel MRI and Biomarkers into Prostate Cancer Active Surveillance Risk Assessment” at DOD IMPACT meeting in Baltimore, MD on August 5, 2016.

7 PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Michael A. Liss, M.D., M.A.S.*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*4.8*
Contribution to Project:	*Oversight: study design / development / implementation*
Funding Support:	

Name:	Kerri Kendrick, P.A.
Project Role:	Clinical Research Coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2.4
Contribution to Project:	IRB approval, patient enrollment, organization of patient MRI and follow up.
Funding Support:	*Department of Urology departmental funds*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Dr. Liss received a 4/8ths VA appointment as of May 31, 2016. This VA appointment is 2/8ths clinical and 2/8th research and thereby provides an additional 20% protected research time. Dr. Liss now has 60% protected research time. Additionally Dr. Liss received DHHS funding from the Agency for Healthcare Research and Quality via R03 HS024810 to which he is committing 0.24 person months. He has also been awarded institutional / departmental funds for several pilot studies he is conducting in order to gather preliminary data for larger grant submissions. His complete active other support is provided in the appendices.

What other organizations were involved as partners?

Organization Name: Audie L. Murphy Veterans Hospital San Antonio
Location of Organization: *San Antonio, Texas*
Partner's contribution to the project *Providing patients for enrollment, supporting protected research time*
In-kind support *Dedicated research time*
Facilities: clinic space for recruitment, use of VA computers

Organization Name: University of California San Diego
Location of Organization: *San Diego, California*
Partner's contribution to the project *Providing sequence data for the generation of the RSI MRI and providing a quality check of the scans.*
Facilities: Multi-model Imaging Laboratory, Off site
Collaboration: David Karow, Nathan White, and Anders Dale

8 SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:
Not Applicable

QUAD CHARTS:
Not Applicable

9 APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text.*

Other Support – Michael Liss
Annotated SOW
Certificate in Translational Research acceptance letter
Prostate MR Imaging Symposium schedule
ARRS CME Transcript
PASS publication
SABOR publication
IMPACT 2016 Poster

Other Support
MICHAEL A. LISS, M.D., MAS
CURRENT

Title	**Transitional Care of Service Members with Genitourinary Injury**
Role	PI
Time Commitments	1%
Supporting Agency	UTHSCSA IIMS Pilot Award
Name & Address of the Funding Agency's procuring Contracting/Grants Officer	Chris G. Green, CPA, Office of Sponsored Programs, 7703 Floyd Curl Drive, San Antonio, TX 78229
Performance Period	09/01/2016-08/31/2017
Level of Funding	$31,560
Brief description of the project's goals List of Specific Aims	This study will be the first to address genitourinary trauma access to care issues and propose solutions regarding veterans transitioning to Veteran's Affairs Health System. Aim 1: To identify the characteristics and access to care patterns of veterans that sustained battlefield genitourinary injuries. Aim 2: To identify areas of improvement in the initial assessments and management of veterans with genitourinary injuries during transition to care in the Veteran's Affairs Health System.
If overlap with other existing and pending research projects; if none state "None"	None

Title	**Prostate MRI as a Screening Tool to Detect Prostate Cancer**
Role	PI
Time Commitments	1%
Supporting Agency	UTHSCSA CTRC CPPS Pilot Award
Name & Address of the Funding Agency's procuring Contracting/Grants Officer	Chris G. Green, CPA, Office of Sponsored Programs, 7703 Floyd Curl Drive, San Antonio, TX 78229
Performance Period	11/01/2014-06/14/2017
Level of Funding	$25,000
Brief description of the project's goals List of Specific Aims	The project is currently assessing novel MRI software to improve cancer detection in men undergoing either their first prostate biopsy or a repeat prostate biopsy in men with low-grade prostate cancer on active surveillance. The novel MRI is faster and does not require IV contrast material. The study compares the new software to traditional multi-parametric MRI to determine if the information obtained is similar or better so that future studies could be less invasive and costly.
If overlap with other existing and pending research projects; if none state "None"	None

Title	**Incorporation of Novel MRI and Biomarkers Into**

	Prostate Cancer Active Surveillance Risk Assessment, W81XWH-15-1-0441
Role	PI
Time Commitments	40%
Supporting Agency	Department of Defense/U.S. Army Medical Research and Materiel Command Congressionally Directed Medical Research Programs
Name & Address of the Funding Agency's procuring Contracting/Grants Officer	Kathy Robinson, Contracting Officer, 301-619-8803, Kathy.e.robinson.civ@mail.mil
Performance Period	09/01/2015 – 06/30/2019
Level of Funding	$561,600
Brief description of the project's goals List of Specific Aims	The award provides salary support to engage in additional training in incorporating translational research into clinical trials. No money is allocated to research endeavors as this is a career development award. A novel MRI is being utilized in men prior to active surveillance biopsy to test accuracy and utility of the novel technique. As the training component I will earn a certificate of translational research from UTHSCA to augment my Masters in Applied Science in Clinical Research. As a mentorship component, Dr. Thompson will guide me in clinical trials research and offer assistance to gain access to SWOG and the workings of current clinical trials. Dr. Fox is the director of the Research Imaging Institute at UTHSCSA and will mentor my imaging component.
If overlap with other existing and pending research projects; if none state "None"	None

Title	**Relationship of the Intestinal Microbiota and Benign prostatic hypertrophy**
Role	PI
Time Commitments	1%
Supporting Agency	UTHSCSA Department of Urology
Name & Address of the Funding Agency's procuring Contracting/Grants Officer	Gabe Hernandez, Vice Dean for Finance, 7703 Floyd Curl Drive, San Antonio, TX 78229
Performance Period	03/01/2016-02/28/2017
Level of Funding	$25,000
Brief description of the project's goals List of Specific Aims	In this proposal we seek to investigate various aspects of intestinal microbiota and its potential influence of BPH as a pilot study for future funding.
If overlap with other existing and pending research projects; if none state "None"	None

Title	**ARLG-ESI: Microbiota Colonization in the Presence of Intestinal Fluoroquinolone Resistant E. coli, UM1 AI104681-04**
Role	PI
Time Commitments	1%

Supporting Agency	Duke University
Name & Address of the Funding Agency's procuring Contracting/Grants Officer	Keri R Baum, Clinical Research Associate Clinical Operations, Antibiotic Resistance Leadership Group (ARLG). Duke Clinical Research Institute (DCRI), 2400 Pratt Street, Durham, NC 27703 Office (919) 668-8681, Keri.baum@duke.edu
Performance Period	06/01/2016-11/30/2017
Level of Funding	$63,000
Brief description of the project's goals List of Specific Aims	Primary object is to identify the relative abundance for 27 genera, which represent a mean bacterial abundance in patients with and without fluoroquinolone resistance.
If overlap with other existing and pending research projects; if none state "None"	None

Title	**Rapid PCR to Guide Antibiotic Therapy at the Time of Prostate Biopsy, R03HS024810**
Role	PI
Time Commitments	2%
Supporting Agency	Agency for Healthcare Research and Quality/DHHS
Name & Address of the Funding Agency's procuring Contracting/Grants Officer	Brian Campbell, brian.campbell@ahrq.hhs.gov, 301-427-1266, 5600 Fishers Lane, Rockville, MD 20857
Performance Period	07/01/2016-12/31/2017
Level of Funding	$100,000
Brief description of the project's goals List of Specific Aims	In this proposal, we evaluate the use of a rapid test to detect the presence of a strain of bacteria that is a major cause of infection after a prostate biopsy.
If overlap with other existing and pending research projects; if none state "None"	None

If overlap with other existing and pending research projects; if none state "None"	None

Training Goals

Major Task 1: *T1 Translational Research*	**Percent Complete Or Tasks Completed**
Subtask 1: Certificate in Translational Research	1/16 Hours Currently enrolled in 3 hrs
Subtask 2: Seminars in Translational Research symposium	Not Attended due to schedule conflicts
Subtask 3: Translational Researcher Awareness Program	10/60 (17%) articles reviewed
Subtask 4: Mentorship of Residents	Resident 1st author manuscripts 1 Accepted 2 Submitted 2 Writing
Subtask 5: Case Presentations at GU Oncology Conference	Every Other Friday
Major Task 2: Clinical Trial Education	
Subtask 1: SWOG Young Investigators Training Course	Not Completed
Subtask 2: **SABOR** biomarker study	Liss et al. OJU Dec 2015
Subtask 3: Prostate Active Surveillance Study (PASS)	Liss et al. PCAN Jul 2016
Major Task 3: MRI Biomarker and Risk Assessment	
Subtask 1: Prostate MR Imaging National Meetings	ARRS 2016 Prostate MR Imaging Symposiumi (Austin, TX 2/26/2016)
Subtask 2: Formal course work in MRI	Not Completed
Subtask 3: Attend the SWOG Imaging Committee	Invited Chicago 9/2016

Mentoring Specific Tasks

Major Task 1: ***Incorporation into leadership roles (Dr. Thompson)***	**Percent Complete Or Tasks Completed**
Subtask 1: Lead CTRC GU Working Group	Complete, Continued
Subtask 2: SABOR data collection and biomarker requests	Complete, Continued
Subtask 2: SWOG GU Committee	Complete, Continued
Subtask 3: PASS Meeting	Complete, Continued
Milestone(s) Achieved: Attendance at Meetings	100% for SWOG, Missed 1 PASS meeting due to sisters wedding.
Major Task 2: ***MRI Image Analysis (Dr. Fox)***	
Subtask 1: Present for acquisition of MRI and data collection	Complete, Continued
Subtask 2: Interaction with Imaging Scientists	Complete, Continued
Milestone(s) Achieved: Give a summary MRI lecture at Grand Rounds	Yearly Starting 1/20/2017

Research-Specific Tasks:

Specific Aim 1: Prostate MRI to predict cancer progression in men on active surveillance	**Percent Complete Or Tasks Completed**
Major Task 1: Clinical trail initiation	
Subtask 1: Complete IRB	Completed
Subtask 2: Incorporate imaging protocols of mpMRI and RSI MRI	Completed
Subtask 3: Patient enrollment	Enrolled 23 Patients
Specific Aim 2: Biomarker testing to predict active surveillance outcomes.	
Major Task 2: Serum PSA, Free PSA, and biopsy tissue collection and storage logistics	
Subtask 1: Serum Banking	With enrollment
Subtask 2: Complete material transfer sheets for NanoString and confirm logistics of transfer.	Completed
Subtask 3: Analysis of PSA biomarkers	Not started
Subtask 4: Identify a target gene for exploration in immunohistochemistry (IHC)	Not Started
Specific Aim 3*:* Incorporation of Imaging and Biomarker data into the PROMISS calculator.	
Major Task 3: Incorporation of Imaging and Biomarker data into the PROMISS calculator.	
Subtask 1: Incorporation of Imaging and Biomarker data into the PROMISS calculator.	Not Started
Subtask 2: Manuscript Preparation	Not Started

December 14, 2015

Michael A. Liss, M.D.
8703 Ledge Run
San Antonio, TX 78255

Dear Dr. Liss:

Congratulations! Your application for admission to the **Certificate in Translational Science (CTS)** program in the Graduate School of Biomedical Sciences at The University of Texas Health Science Center at San Antonio has been approved for **Spring 2016**. In addition, you successfully cleared the security background and sanction check required by Texas law.

The first day of class will be Thursday, January 7, 2016. Tuition and fees will be due in the Bursar's Office by 4:30 p.m. on the day before, January 6, 2016, to avoid a late fee.

In addition, a mandatory orientation is being scheduled by the Office of Student Life. Please contact that office directly at 210-567-2654 for specific details.

It would be advisable for you to discuss your program of study with Dr. Donald Dougherty, Committee on Graduate Studies (COGS) Chair for the Certificate in Translational Science program, well in advance of your registration.

To inform us of your admissions decision, **please complete the attached Statement of Intent and email it to stong@uthscsa.edu as soon as possible, and no later than December 21, 2015.**

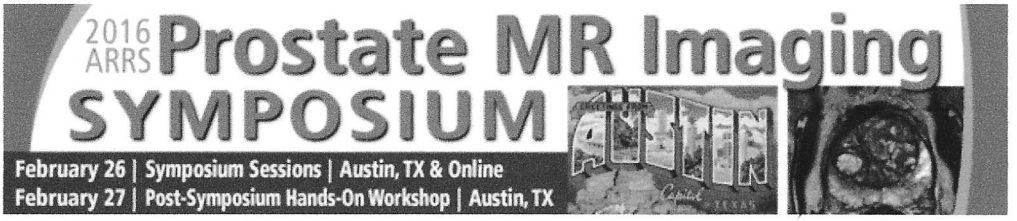
We sincerely hope that you will accept this offer of admission and we look forward to a very exciting and productive interval in your academic experience.

Sincerely,

David S. Weiss, Ph.D.
Dean, Graduate School of Biomedical Sciences

DSW/jms

cc: Dr. Donald Dougherty, COGS Chair and Advisor, Certificate in Translational Science Program
Registrar's Office
Office of Student Life



Schedule

All times reflect the Central Time Zone.

Friday, February 26

SESSION SCHEDULE—IN-PERSON & VIRTUALLY

Time	Session Topic	Faculty
7:00–8:00 am	Registration/Continental Breakfast (In-Person Only)	
8:00–8:15 am	Introduction	*Jelle Barentsz, MD, PhD*
8:15–8:45 am	Prostate Cancer Background (Epidemiology and Pathology)	*Theodorus van der Kwast, MD*
8:45–9:15 am	Prostate Cancer Diagnosis and Treatment Options	*Peter Pinto, MD*
9:15–9:45 am	MR Techniques (1.5T vs 3T, coil selection, patient preparation)	*Rajan Gupta, MD*
9:45–10:15 am	30-Minute Break	
10:15–10:45 am	T2W1-Anatomy, Staging, and TZ Cancers	*Daniel Margolis, MD*
10:45–11:15 am	Multiparametric MR of Prostate—Diffusion Weighted Imaging	*Masoom Haider, MD*
11:15–11:45 am	Dynamic Contrast-Enhanced MRI	*Sadhna Verma, MD*
11:45 am–12:15 pm	PIRADS v.2	*Jelle Barentsz, MD, PhD*
12:15–1:30 pm	75-Minute Lunch Break (On Your Own)	
1:30–2:00 pm	Tips and Pitfalls in Prostate MR	*Andrew Rosenkrantz, MD*
2:00–2:30 pm	MR Incorporations In Screening and AS	*Antonio Carlos Westphalen, MD, PhD*
2:30–3:00 pm	Recurrence Imaging and Management	*Adam Froemming, MD*
3:00–3:30 pm	30-Minute Break	
3:30–4:00 pm	Targeted Biopsy: US Fusion vs. MR in bore	*Peter Pinto, MD, and Dan Sperling, MD*
4:00–4:30 pm	Emerging Focal Therapies	*Jurgen Futterer, MD*

4:30–5:00 pm	Panel Discussion With Question and Answer Session	*All Faculty*
5:00 pm	Adjourn	

This schedule is subject to change.

Register for In-Person Register for Virtual

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ARRS
CME TRANSCRIPT

Report Date: 03/21/2016

Michael Liss
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Customer ID: 744506

Activity Source	Subspecialties	Credit Type	Date	Credits Earned
PROSTATE16/PROSTATE16_01: Introduction	Genitourinary Imaging	CAT1	02/26/2016	0.25
2016 ARRS Prostate MR Imaging Symposium				
PROSTATE16/PROSTATE16_02: Prostate Cancer Background	Genitourinary Imaging	CAT1	02/26/2016	0.25
2016 ARRS Prostate MR Imaging Symposium				
PROSTATE16/PROSTATE16_03: Prostate Cancer Diagnosis and Treatment Options	Genitourinary Imaging	CAT1	02/26/2016	0.50
2016 ARRS Prostate MR Imaging Symposium				
PROSTATE16/PROSTATE16_04: MR Techniques (1.5T vs. 3T, coil selection, patient preparation)	Genitourinary Imaging,Magnetic Resonance Imaging	CAT1	02/26/2016	0.50
2016 ARRS Prostate MR Imaging Symposium				
PROSTATE16/PROSTATE16_05: T2W1-Anatomy, Staging, and TZ Cancers	Genitourinary Imaging	CAT1	02/26/2016	0.50
2016 ARRS Prostate MR Imaging Symposium				
PROSTATE16/PROSTATE16_06: Multiparametric MR of Prostate-Diffusion Weighted Imaging	Genitourinary Imaging,Magnetic Resonance Imaging	CAT1	02/26/2016	0.50
2016 ARRS Prostate MR Imaging Symposium				
PROSTATE16/PROSTATE16_07: Dynamic Contrast-Enhanced MRI	Genitourinary Imaging,Magnetic Resonance Imaging	CAT1	02/26/2016	0.50
2016 ARRS Prostate MR Imaging Symposium				

Customer ID: 744506

Activity Source	Subspecialties	Credit Type	Date	Credits Earned
PROSTATE16/PROSTATE16_08: PIRADS v. 2 2016 ARRS Prostate MR Imaging Symposium	Genitourinary Imaging	CAT1	02/26/2016	0.50
PROSTATE16/PROSTATE16_09: Tips and Pitfalls in Prostate MR 2016 ARRS Prostate MR Imaging Symposium	Genitourinary Imaging,Magnetic Resonance Imaging	CAT1	02/26/2016	0.50
PROSTATE16/PROSTATE16_10: How MRI Can Be Incorporated into Active Surveillance Management Algorithms 2016 ARRS Prostate MR Imaging Symposium	Genitourinary Imaging,Magnetic Resonance Imaging	CAT1	02/26/2016	0.50
PROSTATE16/PROSTATE16_11: Recurrence Imaging and Management 2016 ARRS Prostate MR Imaging Symposium	Genitourinary Imaging	CAT1	02/26/2016	0.50
PROSTATE16/PROSTATE16_12: Targeted Biopsy: US Fusion vs. MR in bore 2016 ARRS Prostate MR Imaging Symposium	Genitourinary Imaging,Magnetic Resonance Imaging,Biopsy	CAT1	02/26/2016	0.50
PROSTATE16/PROSTATE16_13: Emerging Focal Therapies 2016 ARRS Prostate MR Imaging Symposium	Genitourinary Imaging	CAT1	02/26/2016	0.50
PROSTATE16/PROSTATE16_14: Panel Discussion with Question and Answer 2016 ARRS Prostate MR Imaging Symposium	Genitourinary Imaging,Magnetic Resonance Imaging	CAT1	02/26/2016	0.50

Total Credits Earned: 6.50

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Prostate Cancer and Prostatic Diseases (2016) 00, 1–5

www.nature.com/pcan

ORIGINAL ARTICLE

A diagnosis of prostate cancer and pursuit of active surveillance is not followed by weight loss: potential for a teachable moment

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BACKGROUND: Obesity is a risk factor for incident prostate cancer (PC) as well as risk of disease progression and mortality. We hypothesized that men diagnosed with lower-risk PC and who elected active surveillance (AS) for their cancer management would likely initiate lifestyle changes that lead to weight loss.

METHODS: Patients were enrolled in the Prostate Active Surveillance Study (PASS), a multicenter prospective biomarker discovery and validation study of men who have chosen AS for their PC. Data from 442 men diagnosed with PC within 1 year of study entry who completed a standard of care 12-month follow-up visit were analyzed. We examined the change in weight and body mass index (BMI) over the first year of study participation.

RESULTS: After 1 year on AS, 7.5% (33/442) of patients had lost 5% or more of their on-study weight. The proportion of men who lost 5% or more weight was similar across categories of baseline BMI: normal/underweight (8%), overweight (6%) and obese (10%, χ^2 test $P = 0.44$). The results were similar for patients enrolled in the study 1 year or 6 months after diagnosis. By contrast, after 1 year, 7.7% (34/442) of patients had gained $>5\%$ of their weight.

CONCLUSIONS: Only 7.5% of men with low-risk PC enrolled in AS lost a modest ($\geqslant 5\%$) amount of weight after diagnosis. Given that obesity is related to PC progression and mortality, targeted lifestyle interventions may be effective at this 'teachable moment', as men begin AS for low-risk PC.

Prostate Cancer and Prostatic Diseases advance online publication, 19 July 2016; doi:10.1038/pcan.2016.28

INTRODUCTION

Obesity has been associated with increased risk of prostate cancer (PC) progression among patients managed with active surveillance (AS).[1–6] Evidence from animal models suggests that weight loss may improve PC outcomes; however, this has not yet been demonstrated in human clinical trials.[7,8] In addition to a potential reduction in PC progression as well as other morbidities with weight loss, weight reduction may reduce the risk of treatment-related complications (e.g., urinary incontinence) in those men who ultimately require treatment in subsequent years due to disease progression.[3,9,10]

Many patients demonstrate remarkable lifestyle modifications after a diagnosis of low-risk PC.[11,12] These lifestyle changes include improved eating habits, increased daily physical activity and weight loss. Few data exist on the effectiveness of these self-imposed lifestyle modifications that are carried out outside the formal programs. Population-based data suggest limited lifestyle modifications after diagnosis and potentially a reduction in exercise.[13,14]

A diagnosis of cancer is thought to represent a teachable moment for patients, at which time patients would be more likely to adopt healthy lifestyle changes resulting in weight loss. If these types of lifestyle changes are implemented, there may be an impact on cancer progression as well as a reduced risk of cardiovascular complications in the future.[15] We sought to investigate whether a new cancer diagnosis without specific discussion of lifestyle changes led to changes in body mass index (BMI) using the Canary Prostate Active Surveillance Study (PASS), a large, multi-institutional, prospective study of men with localized PC on AS.

MATERIALS AND METHODS

PASS study population

Data are from the PASS, a multicenter, prospective study of men who elected AS for PC management.[16,17] All men provided written informed consent before participation, and study procedures were approved by the local institutional review board for each study site. Men being seen in urology clinics were eligible for PASS if they had clinical stage T1–2 localized PC, no previous cancer treatment, no history of other malignancies (except non-melanoma skin cancer), an Eastern Cooperative Oncology Group status of 0 or 1 and were willing to participate in a structured AS protocol including quarterly PSA measures, semiannual digital rectal examinations and periodic surveillance prostate biopsies. There were no lifestyle or behavioral components as part of the protocol.

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The primary outcomes of PASS are the discovery and validation of biomarkers that predict outcomes to improve management of individual patients with PC.

Data collection, definitions and outcomes

At baseline, participants reported information on race/ethnicity, smoking status (never/former/current), alcohol use in the past year (one or more drinks per month) and family history of PC; clinic staff measured height and weight. BMI was calculated as weight (kg) divided by height (m^2) and was categorized as normal (BMI < 25 kg/m^2), overweight ($25 \leqslant$ BMI < 30 kg/m^2) and obese (BMI $\geqslant 30$ kg/m^2).[18] The primary outcome of this analysis was percentage weight change, calculated as the difference in weight between baseline and year 1 visits divided by weight at baseline visit.

Statistical analyses

Weight loss of 5% or more, a level endorsed by the US Centers for Disease Control and Prevention for improving cardiovascular health (http://www.cdc.gov/healthyweight/losing_weight/index.html), was of particular interest.[18] Weight maintenance was defined as change in weight of $\leqslant \pm 3\%$ relative to baseline. Minimal weight change was defined as ± 3.1–4.9%, and modest weight change was defined as $\geqslant \pm 5\%$, an amount considered clinically meaningful. Weight change from baseline was compared across BMI categories using Fisher's exact tests. Multiple linear regression models were used to evaluate the association of percentage weight change with demographic characteristics, including age (< 55 (reference), 55–64 and 65+ years), race (Caucasian (reference), African-American, Other), BMI (normal (reference), overweight, obese), smoking status (current/former vs never (reference), alcohol intake (< 1 drink per month (reference) vs 1+ drink per month) and family history of PC (no (reference) vs yes). Study site was considered as a random effect in linear mixed models, but was found to neither improve model fit nor markedly change the fixed-effect estimates and therefore was not included in final models. Since the potential for weight change might be greatest among men with newly diagnosed PC, data and analyses are presented separately for the subset of men who enrolled in PASS within 12 months or within 6 months of their PC diagnosis date. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). All statistical hypotheses were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Between September 2008 and February 2015, a total of 745 patients enrolled in PASS and had completed a 12-month follow-up visit. Of these men, 466 enrolled in PASS within 1 year, and 258 within 6 months, of PC diagnosis. Men enrolled later than 12 months from diagnosis or had missing data missing for any of the examined covariates were excluded, leaving 442 men for these analyses, 242 of whom were enrolled within 6 months of diagnosis. Demographic and health-related characteristics of study patients are displayed in Table 1. For the sample of patients enrolled within 1 year of cancer diagnosis, the mean age was 63 years (s.d. = 7), mean weight was 194 pounds (s.d. = 32) and mean height was 70 in (s.d. = 3). Twenty-three percent ($n = 100$) were normal, 52% ($n = 231$) were overweight and 25% ($n = 111$) were obese. Overall, 7.5% ($n = 33$) lost more 5% or more of their body weight after 1 year. The distribution of demographic characteristics among the subset of patients enrolled within 6 months of their diagnosis was similar to the overall study sample. While men with a BMI < 25 kg/m^2 lost on average 0.1 pounds (s.d. = 4.0), overweight and obese men gained 0.4 pounds (s.d. = 3.7) and 0.1 pounds (s.d. = 4.3), respectively, over the year after diagnosis.

Figure 1 shows the proportion of patients, for both the overall study sample and by BMI group, who lost, maintained or gained weight during the first year of study enrollment after PC diagnosis. In the overall sample of patients enrolled within 1 year of cancer diagnosis (Figure 1a) and the subset of patients enrolled within 6 months of cancer diagnosis (Figure 1b), the majority of men maintained their enrollment weight (65% and 61% changed weight by ± 3% or less, respectively). Among the overall sample of patients enrolled within 12 months of PC diagnosis, similar proportions lost or gained $> 5\%$ of their enrollment weight during the first year of study (7.5% and 7.7%, respectively; Figure 1a). A greater proportion of obese men had a weight loss of $\geqslant 5\%$ compared with overweight or normal/underweight men (9.9% vs 6.1% and 8.0%, respectively), and a similar pattern was seen for weight gain of $\geqslant 5\%$ (9.9 vs 8.2% and 4.0%, respectively), although the differences in weight gain $\geqslant 5\%$ across baseline BMI categories was not statistically significant (Fisher's exact test *P*-value = 0.24).

Among the subset of 242 patients who enrolled within 6 months of PC diagnosis, a slightly greater proportion of men lost or gained $\geqslant 5\%$ of enrollment weight, compared with men who enrolled within 12 months of PC diagnosis (9.1% vs 7.5% with modest loss and 9.1% vs 7.7% with modest gain, respectively). In addition, the proportions of obese, overweight and normal/underweight men who lost $\geqslant 5\%$ weight were slightly greater among the subset of patients enrolled within 6 vs 12 months of diagnosis (12.9% vs 9.9% for obese, 7.1% vs 6.1% for overweight and 9.4% vs 8.0% for normal weight, respectively).

Among the 442 patients who enrolled within 1 year of diagnosis, none of the baseline variables significantly predicted weight

Table 1. Demographics of the study cohort

Demographics	*Diagnosed within 1 year of enrollment* N *(%) or mean (s.d.)*	*Diagnosed within 6 months of enrollment* N *(%) or mean (s.d.)*
	N = *442*	N = *242*
Age (years)	63 (7)	634 (7)
< 55	57 (13)	22 (9)
$55 \leqslant$ Age < 65	182 (41)	106 (44)
$\geqslant 65$	203 (46)	114 (47)
Race		
Caucasian American	384 (87)	206 (85)
Hispanic/Latino	20 (5)	12 (5)
African American	19 (4)	10 (4)
Asian	12 (3)	9 (4)
Other	7 (1)	5 (2)
Weight, baseline (pounds)	194 (32)	195 (32)
Height, baseline (in)	70 (3)	70 (3)
BMI (kg/m^2)		
< 25	100 (23)	53 (22)
$25 \leqslant$ BMI < 30	231 (52)	127 (52)
$\geqslant 30$	111 (25)	62 (26)
Lost 5% body weight	33 (7)	22 (9)
Cigarette use		
Current	17 (4)	7 (3)
Former	172 (39)	101 (42)
Never	253 (57)	134 (55)
Alcohol use (in past 12 months)		
Yes	370 (84)	198 (82)
No	72 (16)	44 (18)
Family history of PC		
Yes	111 (25)	65 (27)
No	331 (75)	177 (73)

Abbreviations: BMI, body mass index; PC, prostate cancer. Results are shown for all participants diagnosed with PC within 1 year before study enrollment and a subset of those diagnosed within 6 months before enrollment.

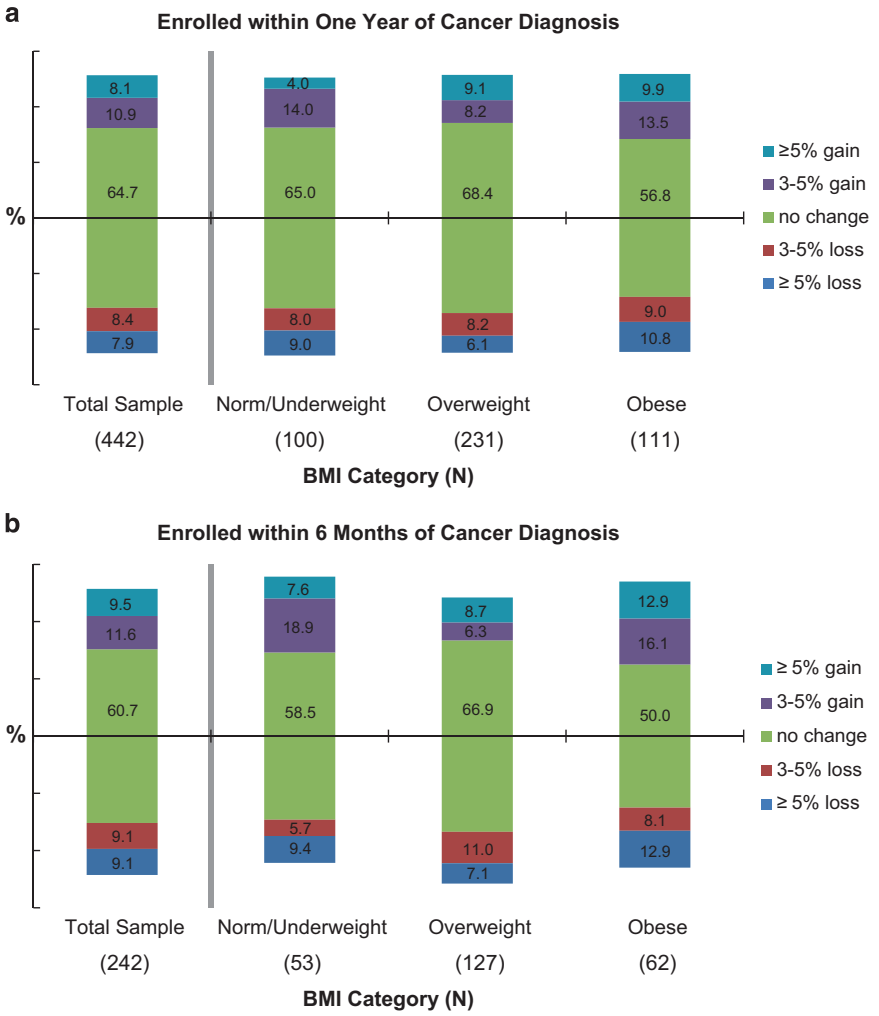

Figure 1. Change in weight during first year of enrolment in a active surveillance protocol. Results are shown for the total cohort and by body mass index (BMI) category, both for all participants enrolled in the study within 1 year of cancer diagnosis (**a**) and for those enrolled within 6 months of cancer diagnosis (**b**).

change (Table 2). In the subset of patients who enrolled within 6 months of diagnosis, men who had a family history of PC or did not regularly consume alcohol tended to lose more weight compared with men who did not have a family history of PC or were regular drinkers, although these differences were neither clinically nor statistically significant (Table 2).

DISCUSSION

In a sample of men with newly diagnosed, early-stage PC enrolled in an AS study, of whom three-quarters were overweight or obese, we found little evidence to suggest that men made lifestyle changes that resulted in weight loss during the 1-year period following enrollment in an AS study. The majority of men (286/442, 65%) maintained their enrollment weight ($\leqslant \pm 3\%$), and only 7.5% of men lost 5% weight or more during the first year of AS. As troublesome, but perhaps not surprising, was the observation that a nearly equivalent number of men *gained* 5% or more from their enrollment weight (34/442, 7.7%) over the ensuing year.

These findings are consistent with those recently noted in a subset ($n = 511$) of the Prostate Testing for Cancer and Treatment (PROTECT) trial in the United Kingdom in which no change in BMI after a diagnosis of PC was found.[19] No change in BMI was noted in this cohort despite ~1/3 of men modifying their behavior after their cancer diagnosis by reducing alcohol intake, quitting smoking or increasing physical activity without deliberate intervention.[12,19] Men in the PC Prevention Trial (PCPT) overall only gained 1–2 lbs on average over the 7 years; however, the most at risk group for weight gain was men with low-grade cancer (71% higher annual weight gain than men with no cancer, $P = 0.002$).[20] This indicates men with a low grade PC diagnosis may actually be at risk for weight gain. Preliminary evidence suggests that small lifestyle modifications may make a difference in PC outcomes. For instance, in the Health Professionals Follow-up Study, a modest amount of vigorous activity for $\geqslant 3$ h a week was associated with lower overall and PC-specific mortality.[21]

A diagnosis of PC, even when 'low risk', can be a psychologically traumatizing event.[22] We sought to determine whether men make lifestyle changes that would result in weight loss. With the growing evidence that cancer-specific survival for men with low-risk PC on AS is remarkably high (98% or more), we further wondered if behavioral change and weight loss could contribute to these outcomes.[3,23]

The majority of men in this large prospective PC AS study had either not changed, or *increased*, their weight within 1 year after diagnosis. This striking observation supports the opportunity for a 'teachable moment' at the time of PC. Certainly, the simplest

Table 2. Association between weight change and patient characteristics

Baseline demographics	*Diagnosed within 1 year of enrollment (N = 442)*			*Diagnosed within 6 months of enrollment (N = 242)*		
	Mean baseline weight (lb)	*Weight change (lb) from baseline to year 1*	P-*value*[a]	*Mean baseline weight (lb)*	*Weight change (lb) from baseline to year 1*	P-*value*[a]
Age (years)						
< 55	194	0.26 (0.63)		190	− 0.19 (1.02)	
55 ⩽ Age < 65	200	0.26 (0.48)	0.59	200	− 0.53 (0.72)	0.94
⩾ 65	189	− 0.13 (0.46)		191	− 0.53 (0.67)	
Race						
African American	197	0.62 (0.91)		202	− 0.37 (1.39)	
Caucasian	194	-0.19 (0.31)	0.67	195	− 0.32 (0.47)	0.97
Other	192	-0.04 (0.67)		194	− 0.55 (0.92)	
Body mass index						
Under/normal	162	− 0.40 (0.61)		162	− 0.90 (0.90)	
Overweight	190	0.33 (0.49)	0.40	191	− 0.75 (0.74)	0.41
Obese	232	0.46 (0.61)		232	0.41 (0.90)	
Smoking status						
Current/former	197	0.29 (0.48)	0.40	199	− 0.08 (0.73)	0.24
Never	192	− 0.04 (0.45)		192	− 0.74 (0.65)	
Alcohol intake (prior year)						
1+ drink per month	196	0.47 (0.40)	0.18	197	0.21 (0.60)	0.09
< 1 per month	188	− 0.21 (0.57)		186	− 1.03 (0.84)	
Family history of PC						
Yes	198	− 0.07 (0.50)	0.36	198	− 0.88 (0.76)	0.13
No	193	0.33 (0.45)		194	0.05 (0.65)	

Abbreviations: LS, least square; PC, prostate cancer. Weight change is recorded as LS means and s.e. from linear regression model.[a]*P*-value from Type 3 test, which tests the significance of each variable in the model, given all other variables in the model. Regression models are adjusted for baseline weight.

opportunity occurs if the patient decides to pursue a strategy of AS in which no other elements of his life change. However, weight loss and dietary changes surrounding other PC therapies may also be beneficial.[24]

There is no single best method to achieve weight loss; however, elements that are important for clinical success mentioned by the National Heart, Lung and Blood Institute (NIH) include setting goals that are specific, doable and forgiving.[25] They give an example of a goal that meets these requirements, such as 'walk 30 min, 5 days each week' (https://www.nhlbi.nih.gov/health/educational/lose_wt/behavior.htm). This pointed information at the time of low-grade cancer diagnosis could be helpful to evoke behavioral change.

Men on AS for PC have a very low disease-specific mortality rate, and instead have a higher risk of death from competing causes. As a result, this moment is when the clinician can explain to the patient that lifestyle changes that reduce the risk of other causes of death (e.g., myocardial infarction, stroke, diabetes) would have a far-greater impact on health than interventions related to PC.[26,27,25,13] This study and the PROTECT trial show that overweight or obese men on AS are unlikely to modify their lifestyle and lose weight. Recently, the American Society of Clinical Oncology has established an initiative, which includes providing tools and resources for providers and patients regarding obesity including access to weight loss programs for cancer survivors.[28] Formal programs to provide support should be a component of follow-up plans for men on AS.

Only 7.5% of men embarking in a program of AS for low-risk PC had a modest amount of weight loss of at least 5% reduction from baseline weight. Physician facilitated multidisciplinary weight loss programs for all patients on surveillance for prostate cancer should be further investigated.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

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Prevalence of Isolated "Pre-Malignant" Lesions on Prostate Biopsy in a Racially Diverse Community Screened Cohort

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Abstract

Objective: We investigated rates of prostate cancer (PCa), high-grade prostatic intraepithelial neoplaisa (HGPIN) and atypical small acinar proliferation (ASAP) in a multiethnic cohort. Methods: We evaluated prostate biopsy outcomes in men enrolled in the San Antonio Center of Biomarkers of Risk for prostate cancer (SABOR) prospective, observational study. PCa-free men underwent annual PSA testing over nearly 14 years with biopsies based on community standards. We investigated biopsy outcomes with a special interest in rates of cancer, HGPIN, and ASAP. Results: We identified 975 prostate biopsies in 801 subjects from 3/1/2001 to 1/9/2014. PCa, HGPIN, or ASAP was encountered in 28.8% (281/975), 10.1% (98/975), and 5.2% (51/975) of prostate biopsy specimens, respectively. The most significant risk factor for a PCa diagnosis was African American race (OR 5.0, 95% CI: 2.2 - 11.4, p < 0.001). HGPIN and ASAP occurred more commonly in association with PCa (both p < 0.001). We identified 57% (24/42) of men diagnosed with a "pre-malignant" lesion on prostate biopsy and had a subsequent biopsy. Of those only 8% (2/24) were diagnosed with prostate cancer (both Gleason 3 + 3) within 1 year of the initial biopsy. Conclusion: We note a 5-fold increased risk of PCa for African American men. The incidence of HGPIN and ASAP are consistent with previously reported incidence. If diagnosed in isolation, repeat biopsy within one year could be delayed or eliminated as it may not change prostate cancer outcomes.

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Keywords

Active Surveillance, Ethnicity, Prostate Biopsy, Prostate Cancer, Race

1. Introduction

Prostate cancer (PCa) is the most common solid organ malignancy in men with over 230,000 new cases expected in 2015 in the United States alone [1]. Transrectal ultrasound-guided systematic prostate biopsy is the most common means of diagnosing PCa with over 1 million performed annually in the United States [2] [3]. The proportion of men diagnosed with prostate cancer by prostate biopsy ranges between 27% - 40%, though it is affected by a number of variables [4] [5].

Race and ethnicity are directly related to prostate cancer risk and outcomes following treatment; however, some pathologic findings are also concerning for future risk of prostate cancer [6] [7]. The prevalence of two putatively premalignant lesions, high-grade prostatic intraepithelial neoplaisa (HGPIN) and atypical small acinar proliferation (ASAP), among different racial and ethnic groups has not been well characterized, especially in U.S. population-based studies [8]. Most studies to date have focused on the disproportionate risk of prostate cancer among African Americans and limited data are available on the rates of premalignant lesions in Hispanics, the largest and fastest-growing minority in the United States [9].

Hispanic men have similar rates of diagnosis and death from prostate cancer as non-Hispanic Whites, but are poorly-represented in clinical trials [10] [11]. The San Antonio Center of Biomarkers Of Risk for prostate cancer (SABOR) is a community based biomarker discovery and validation study that has followed a prospectively-enrolled cohort with minority race/ethnicity oversampling since 2001; long-term follow-up is available in over 3000 men. Taking advantage of this cohort, we examined rates of prostate cancer, HGPIN, and ASAP to better understand how these rates correlated with overall rates of PCa and PCa aggressiveness in these populations.

2. Methods

2.1. Study Population

The San Antonio Center of Biomarkers Of Risk for prostate cancer (SABOR) is an Institutional Review Board approved Clinical Validation Center of the Early Detection Research Network of the National Cancer Institute. Since 2001, SABOR has recruited 3651 prostate cancer-free men at six sites into a longitudinal study. Data from prostate biopsies prompted by the study or performed prior to study enrollment are collected. Central pathology review was not performed. All biopsy reports were reviewed for presence of ASAP or HGPIN.

2.2. Statistical Analysis

The primary outcome of this study was the specific finding at prostate biopsy that included: PCa, ASAP, or HGPIN. Each prostate biopsy was treated as an independent event; however, a sub-analysis of only those men with a single prostate biopsy was performed due to different pre-test probabilities for cancer, depending on number of prior biopsies. Demographic data were analyzed using the un-paired two-tailed Student's t-test for continuous variables and the Pearson chi-squared test or Fisher's Exact test for binary variables. The difference in pathologic findings across the three racial/ethnic groups was examined using an analysis of variance (ANOVA) test. As the primary outcomes were binary, logistic regression was used in multivariable analysis. Variable selection was obtained by backward elimination using likelihood ratios. Statistical analysis was performed using SPSS v.21 (IBM, Chicago, IL, USA).

3. Results

3.1. Subjects and Overall Pathology Findings

We identified 975 prostate biopsies in 801 SABOR cohort subjects with complete pathology from men enrolled between 3/1/2001 to 1/9/2014; of these, repeat prostate biopsies accounted for 17.8% (174/975). The racial/

ethnic distribution of the biopsies was 60.0% (580/975) Non-Hispanic White, 28.0% (272/975) Hispanic White, and 12.6% (123/975) African American. Study subject demographics are displayed in **Table 1**. Notable differences among racial/ethnic groups included that Hispanics had higher BMI ($p < 0.001$) and African American men were younger ($p < 0.001$). The number of biopsy cores obtained was not different among racial/ethnic groups with a median of 12 cores (ANOVA $p = 0.600$). Prostate cancer, HGPIN, or ASAP and were noted in 28.8% (281/975), 10.1% (98/975), and 5.2% (51/975) of prostate biopsy specimens, respectively. **Figure 1** (initial) and **Figure 2** (repeat) display prostate biopsy pathology results by race and ethnicity.

3.2. Prostate Cancer

Of the 975 prostate biopsies, PCa was found in 29.1% (233/801) of initial and 27.6% (48/126) of repeat biopsies. Low-grade (Gleason 6 or less) cancer was the most common cancer diagnosis in all groups with non-Hispanic Caucasian, Hispanic Caucasians, and African Americans having similar rates: 61.5%, 61.4%, and 62.3%, respectively ($p = 0.817$). Variables predicting cancer presence at biopsy included African American race ($p = 0.001$), age ($p = 0.002$), presence of HGPIN ($p \leq 0.001$), and presence of ASAP ($p = 0.027$). Controlling for serum prostate specific antigen (PSA) levels, BMI, and prostate volume in multivariable logistic regression, the most significant factor for a prostate cancer diagnosis was African American race with an odds ratio of 5.0 (95% CI: 2.2 - 11.4, $p < 0.001$). No difference was found in risk of prostate cancer between non-Hispanic Caucasian and Hispanic Caucasian men ($p = 0.874$).

3.3. High Grade PIN

HGPIN was found in 9% (72/801) of the initial biopsy specimens and in 14.9% (26/174) of repeat biopsies (Fisher's Exact, $p = 0.025$). HPIN alone was diagnosed in 3.4% (15/473) of initial biopsies and 5% (5/100) of repeat biopsies. HGPIN was more likely to be diagnosed when prostate cancer was detected concurrently (19.6%, 55/281) as compared to when no cancer was found on biopsy (6.2%, 43/651) ($p < 0.001$). There was no significant difference in the incidence of HGPIN among racial or ethnic groups: Non-Hispanic Caucasian 10.3% (60/580), Hispanic Caucasians 10.3% (28/272) African American 8.1% (19/123) ($p = 0.750$). In univariable analysis, larger prostate volume ($p = 0.049$), age ($p = 0.004$), and presence of prostate cancer ($p < 0.001$) were significant variables for a higher risk of HGPIN.

Table 1. Demographics (N = 975 biopsy results).

Demographic	White N (%) or median (IQR) N = 580	Hispanic N (%) or median (IQR) N = 272	African American N (%) or median (IQR) N = 123	p value
Age	65 (60 - 70)	64 (58 - 68)	62 (56 - 67)	<0.001
Body mass index	27 (25 - 30)	29 (26 - 31.5)	29 (27 - 32)	<0.001
Prostate specific antigen (ng/mL)	3.2 (1.7 - 4.8)	3.5 (1.9 - 5.2)	3.1 (1.8 - 4.7)	0.916
Number of biopsy cores	12 (11 - 12)	12 (10 - 12)	12 (11 - 12)	0.600
Prostate volume (cc^3)	27 (36 - 54)	34 (24 - 47)	38 (25 - 51)	0.614
Prostate cancer	169 (29.1)	70 (25.7)	42 (34.1)	0.224
Gleason 6	104 (61.5)	43 (61.4)	28 (66.7)	0.817
Gleason 7+	65 (38.5)	27 (38.6)	14 (33.3)	
High grade PIN	60 (11.6)	28 (11.5)	10 (9.7)	0.856
Atypical small acinar proliferation	36 (6.9)	13 (5.3)	2 (3.9)	0.131*

*Linear association p = 0.05.

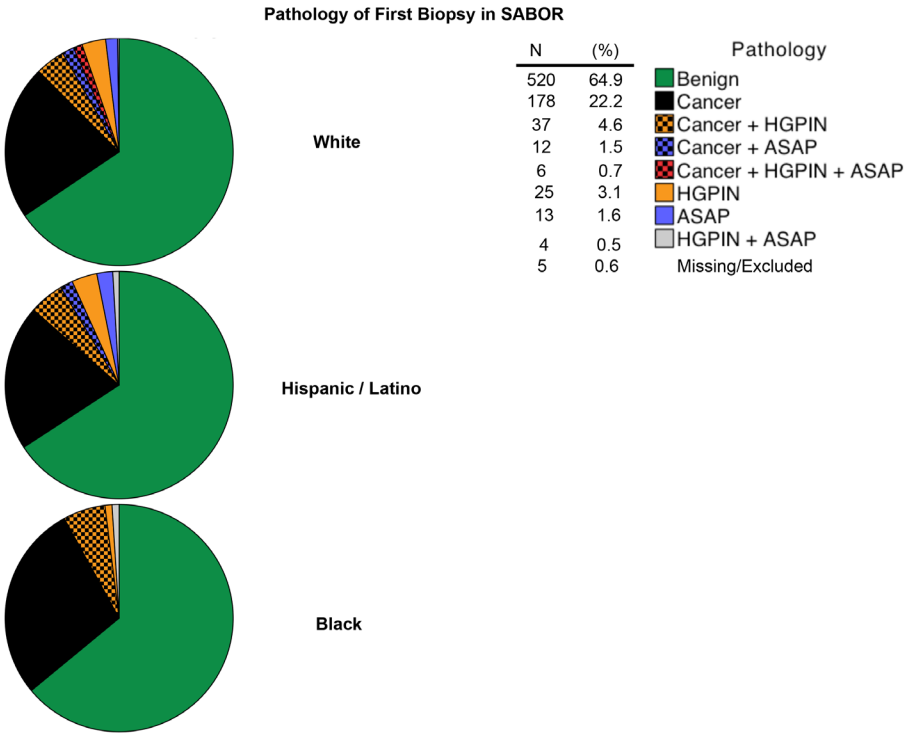

Figure 1. Pathology of first biopsy documented in SABOR database. A pie chart graphically represents the pathologic outcomes of the first documented prostate biopsy among SABOR participants. Eight colors represent the various combinations of benign, malignant, ASAP, and HGPIN.

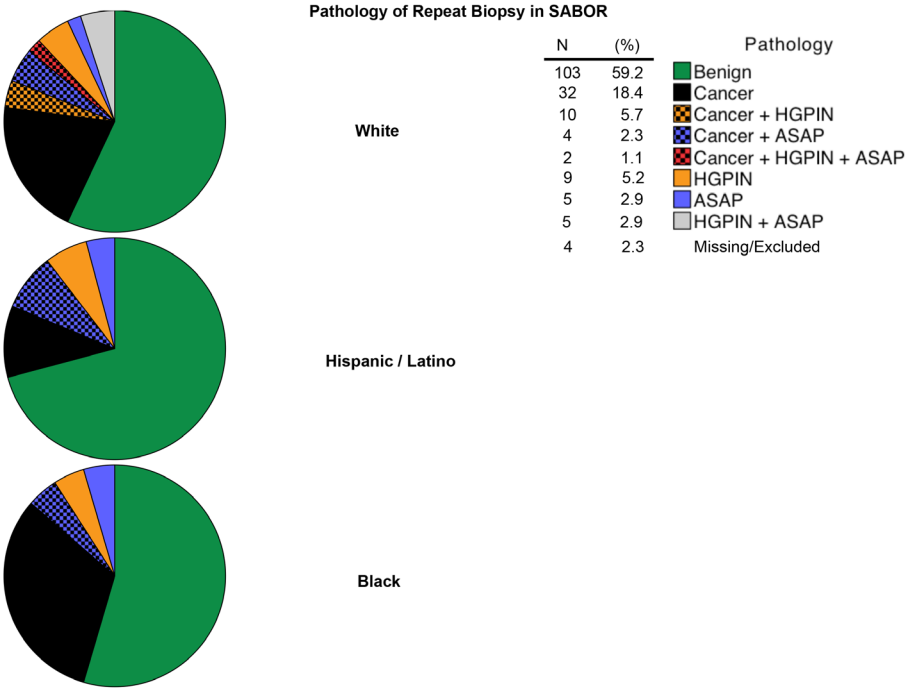

Figure 2. Pathology of repeat biopsy documented in SABOR database. A pie chart graphically represents the pathologic outcomes of the repeated prostate biopsies documented prostate biopsy among SABOR participants. Eight colors represent the various combinations of benign, malignant, ASAP, and HGPIN.

3.4. Atypical Small Acinar Proliferation

ASAP was diagnosed in 4.4% (35/801) of biopsies and 9.2% of repeat prostate biopsies 9.2% (16/174) (Fisher's Exact p = 0.010). ASAP was more likely to be diagnosed with concurrent PCa [8.5% (24/281)] than in isolation [3.9% (27/694)] (p = 0.003). We found no statistical difference in the incidence of ASAP on prostate biopsy when examined by race/ethnicity: non-Hispanic Caucasians 6.2% (36/580), Hispanic Caucasians 4.8% (13/272), and African American 1.6% (2/121) (p = 0.108, p for trend 0.040). Of interest, ASAP did appear less-common among African Americans. Variables positively associated with ASAP included age (p = 0.001) and prostate cancer (p = 0.027) with a trend related to higher prostate volume (p = 0.060).

3.5. Repeat Biopsy after ASAP or HGPIN

We identified only 57% (24/42) of men diagnosed with a "pre-malignant" lesion on prostate biopsy had a subsequent biopsy. The "pre-malignant" lesions included: HGPIN (n = 11), ASAP (n = 9), or HGPIN + ASAP (n = 4) (**Table 2**). Of men diagnosed with ASAP or ASAP/HGPIN alone on a biopsy without a previous diagnosis of prostate cancer, 8/13 had a prostate biopsy within 1 year; however, only 2 were diagnosed with PCa on the repeat biopsy and both cancers were low-grade (Gleason 3 + 3). Eventually, 7/11 men were diagnosed with PCa at

Table 2. Patients with isolated HGPIN or ASAP that underwent repeat biopsy.

Race	Initial pathology	Repeat biopsy within 1 year	Cancer	Gleason	Years to cancer diagnosis	Number of biopsies
Mexican	ASAP	x	Cancer	3 + 4	8.06	2
White	ASAP	x	Cancer	3 + 3	10	2
White	ASAP	Cancer	Cancer	3 + 3	1.12	2
White	ASAP	Negative	Cancer	3 + 3	3.2	4
White	ASAP	Negative	Cancer	3 + 3	6.01	3
Mexican	ASAP	Negative				2
White	ASAP	Cancer	Cancer	3 + 3	0.73	4
Mexican	ASAP	Negative				5
Mexican	ASAP	Negative				2
White	ASAP/HGPIN	x	Cancer	3 + 3	5.46	2
White	ASAP/HGPIN	x				2
Mexican	ASAP/HGPIN	x				2
White	ASAP/HGPIN	Negative				4
Black	HGPIN	x	Cancer	3 + 3	2.26	3
White	HGPIN	x				3
White	HGPIN	Negative				4
Mexican	HGPIN	x				3
Puerto Rican	HGPIN	x				2
White	HGPIN	x				2
Mexican	HGPIN	x				2
White	HGPIN	Negative	Cancer	4 + 5	1.84	4
White	HGPIN	x				4
Black	HGPIN	Negative	Cancer	3 + 3	1.72	3
White	HGPIN	ASAP	Cancer		3.8	4

a median of 5.5 years (range 0.7 - 10.0 years). For men with HGPIN alone, 5/11 had another biopsy within one year with no cancer diagnosis. Eventually, 2/11 men were diagnosed with prostate cancer at a median of 2 years (1.7 - 3.8 years) from the biopsy with HGPIN (**Table 2**).

4. Discussion

The overall diagnostic rate for premalignant lesions not associated with overt prostate cancer remained low, though clinically significant (4.3%, 42/975). Extrapolating this data to an estimated 1 million biopsies are performed in the United States each year, a "pre-malignant" diagnosis could affect nearly 43,000 men per year. Our data provide further support to concerns that HGPIN or ASAP have either a small or no impact on intermediate prostate cancer outcomes. Others have suggested that rates of HGPIN, atypical, non-definitive diagnoses, and low-grade cancer could correlate with diagnostic habits [12]. Therefore, our data suggest that there may be little benefit from standardized repeat biopsy recommendations based on the diagnosis of ASAP or HGPIN in isolation on prostate biopsy. In our study, most of these patients were not diagnosed with cancer on a biopsy performed within one year of the diagnosis of HGPIN or ASAP, suggesting these biopsies could likely be delayed or eliminated. Perhaps more importantly, if PCa was diagnosed, most were low grade, tumors that benefit little from detection or treatment [13]. Our findings are in contrast to previously recommendations for extended biopsies or even prostatectomy for these pathologic entities due to reportedly higher rate of associated cancer, albeit largely low-grade [14] [15]. Given the significant attention given to over-detection (and thus overtreatment as well) of prostate cancer, our data provide support to a more conservative approach to HGPIN and ASAP.

The SABOR cohort is a unique resource for examining prostate cancer risk and characteristics in an aging, multi-ethnic, multi-racial population, one that better mirrors U.S. outcomes than studies from Urology practices that may be affected by referral patterns and often have more homogeneous racial/ethnic demographics. SABOR has facilitated examination of many differences among racial and ethnic groups [12] [16] [17]. The observation of the dramatically higher risk of prostate cancer among African American men is consistent with national data [1]. Of interest is the slightly-lower detection rate of prostate cancer (25.7%) among other racial/ethnic groups [3] [4].

We sought to explore pathologic outcomes in a more detailed fashion. In this analysis, the incidence of HGPIN and ASAP did not vary substantially among racial and ethnic groups. Curiously, while African American men had higher rates of cancer, although not significant, a measurably lower rate of ASAP was found in these men in SABOR. We did confirm our previous observation from the Prostate Cancer Prevention Trial that age has a significant effect on the risk of prostate cancer [18].

At the prostate cancer level, these data confirm the importance of focusing early detection efforts on African American men. We have previously demonstrated the importance of the PCPT Risk Calculator to incorporate this variable in decision-making for prostate biopsies due to the significantly greater risk of cancer and of high-grade prostate cancer in this racial group [19].

There are several limitations to this study including the lack of central pathologic review and a relatively small number of African American men. Regarding the former, our data become more generalizable as a broad range of nuance of pathologic interpretation was operational. Regarding the later, a major study strength is the broad range of races/ethnicities included, especially Hispanic men who are underrepresented in these studies and constitute the fastest growing ethnic group in the U.S. A major strength of this study was the prolonged follow-up.

5. Conclusion

In this population-based cohort study with prolonged follow-up, we found a 5-fold increased risk of prostate cancer in African American men. HGPIN and ASAP were common pathologic findings but were unassociated with risk of prostate cancer.

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Conflict of Interest

None.

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Incorporation of Novel MRI and Biomarkers into Prostate Cancer Active Surveillance Risk Assessment

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ABSTRACT

Background and objectives
Active surveillance is strategy used to monitor low risk prostate cancer in order to delay or avoid aggressive therapies with the option to intervene yearly in the disease process of progression in detected with curative intent. Unfortunately, the initial and secondary prostate biopsies suffer from a 30% sampling error. Progression is usually detected by repeating the prostate biopsy, in some cases yearly. Prostate biopsies can cause significant pain, bleeding, infection, and anxiety. The primary objective of this project is to investigate if a novel screening MRI can predict prostate biopsy outcomes and eventually replace the prostate biopsy as the primary means to follow patients. The secondary purpose is to use biomarkers from blood, urine, or prostate tissue to identify those men who are likely to progress on active surveillance.

Methods
Our primary population is men who are diagnosed with prostate cancer and choose active surveillance. We plan to enroll 160 subjects to undergo a prostate MRI prior to their TRUS prostate biopsy. Both conventional MRI with IV gadolinium contrast and Restriction Spectrum Imaging (RSI) techniques will be employed. Images will be evaluated using a five-point scale (PI-RADS) to determine suspicion of clinical significant prostate cancer. PI-RADS will also be used to grade the RSI images with secondary radiology review. After the MRI, the patient will undergo targeted and template prostate biopsy and pathology compared to PIRADS. Other study endpoints will include Gleason 6 tumor (low-grade) or a negative biopsy. After pathologic review the paraffin embedded tissue will be sent the CPDR in Rockville, MD Aim 2b NanoString technology investigation.

Results to date
To date we have completed the IRB protocol and attained approval for imaging in men undergoing active surveillance for prostate cancer and have an upcoming prostate biopsy. We have enrolled 19 subjects to obtain an MRI and undergo cognitive or MRI-Fusion targeted prostate biopsy from 2/1/2016 to present. Of these men 9 men have completed their biopsy, 4 men have had an MRI and are scheduled for biopsy and 2 men are pending their MRI. Two men have dropped out of the study as screening fails at the MRI scanner (Elevated creatinine and Claustrophobia). Three scans showed "No suspicious lesions" and 66% (2/3) were completely negative and one had 1 core of low grade, low volume prostate cancer (Gleason 3+3, 5% of the core). Three targeted biopsies were negative in the targeted lesions with all having PIRADS scores of 3. In these samples, the standard 12 core biopsy only revealed a "missed lesion" in 1 patient with one core of Gleason 3+3 (<5% of the core). One PIRADS 4 lesion had a positive target with Gleason 3+3 (80% of the core) and a positive 12 core (same Gleason) and a PIRADS 5 that showed Gleason 4+4.

Conclusions
We have successfully implemented our Prostate MRI study at the University of Texas HSC San Antonio. From our preliminary results, PIRADS 4 and 5 lesions are more significant finding on prostate biopsy. PIRADS 3 lesions on MRI are commonly negative on biopsy.

Impact statement
Our research is directed towards improving the quality of life of prostate cancer patients in the form of reduction of prostate biopsies and more accurate selection of active surveillance candidates.

Specific Aims

Aim 1: **Prostate MRI to predict Progression on Active Surveillance.**
Aim 2: **Biomarker testing to predict active surveillance outcomes.**
- **2a) PSA Density and %free PSA as readily available tests to predict cancer progression.**
- **2b) CDPR Nanostring technology to systematically investigate prostate cancer associated genes.**

Aim 3: **Incorporation of Imaging and Biomarker data into the PROMISS calculator.**

OBJECTIVES

[1] to improve the ability to appropriately select candidates to safely choose active surveillance as a prostate cancer management strategy.

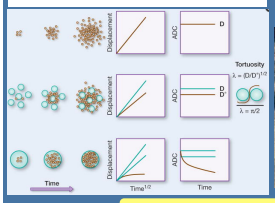
[2] to improve current monitoring for progression of prostate cancer.

Preliminary Data

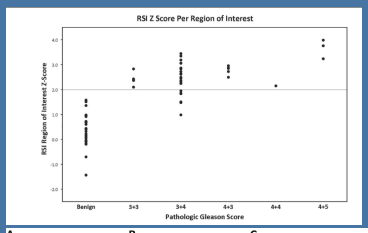
Restriction Spectrum Imaging

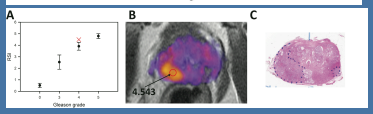
ADC
1. Nonspecific: Not specific for restricted diffusion
2. Hemorrhage and inflammation can lead to falsly low ADC values
3. Spatial distortion

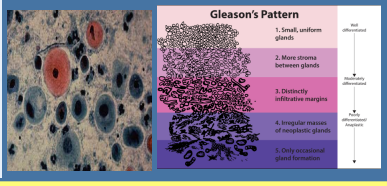
RSI
1. Transverse relaxation rate of the cell decreases with large nuclei in cancer cells.
2. RSI signal in cancer is weighted on the transverse relaxation rate of the nuclear volume.
3. High B values filters out signal from hindered extracellular water
4. B0 Distortion correction (reverse phase encoding (distortion is 180 degrees opposite)



Gleason Grade

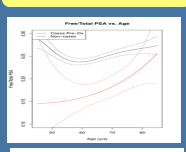


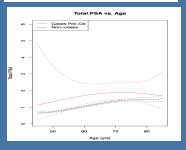




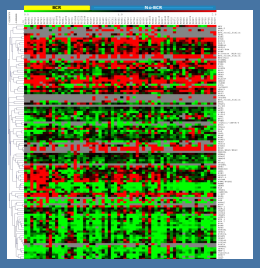
Biomarkers

% Free PSA

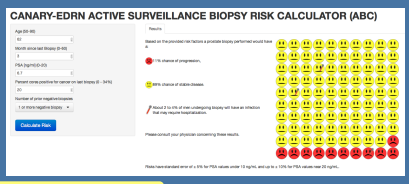




NanoString

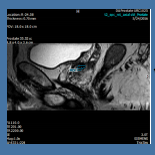


CANARY-EDRN ACTIVE SURVEILLANCE BIOPSY RISK CALCULATOR (ABC)

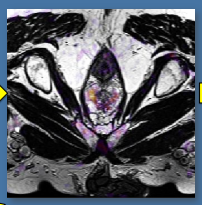


Methods

MRI

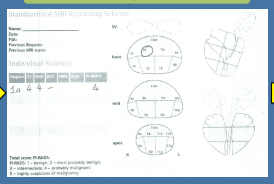


RSI

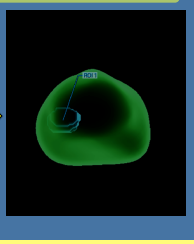


PIRADS

Radiologist Read



Targeted Biopsy



RESULTS

	False Positive	False Negative	True Positive	True Negative
	4	1	6	2
Gleason	6 (5%), Pirads 3	6 (10%)	3+3 15%, Pirads 4	
	neg, Pirads 4		3+3 10%, Pirads 4	
	neg, Pirads 3		3+3, Pirads 3	
	neg, Pirads 3		4+4, Pirads 4	
			4+4, Pirads 5	

CONCLUSIONS

1. **First Year**
   a. **Implementation of novel MRI at a new institution**
   b. **Enrolled 20 subjects**
   c. **Undergoing full RSI processing and will have radiology re-review**
2. **Next**
   a. **Automation of RSI**
   b. **Compare RSI vs. DCE**
   c. **Start analysis of pathologic tissue for nanostring**